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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,871	09/07/2006	Dan Peters	2815-0269PUS2	4256

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EXAMINER	
RAHMANI, NILOOFAR	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
06/25/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/591,871	PETERS ET AL.	
	Examiner	Art Unit	
	NILOOFAR RAHMANI	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/08/2008 and 09/07/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-38 are currently pending in the instant application and claim 39 is cancelled.

Priority

2. This application was filed on 09/07/2006, which is a 371 of PCT/EP05/52107, filed on 05/10/2005, which claims benefit of 60/572,099, filed on 05/19/2004, which claims the priority of DENMARK 2004 00799, filed on 05/19/2004.

3. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e)

the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", In re Rainer, 146 USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is not found in the instant application. c) There is no working example of a prodrug of a compound the formula (I). d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning

pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596. in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim1as well as the presently unknown list of potential prodrug derivatives embraced by claim1.

4. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims.
2) The nature of the invention,
3) The state of the prior art,
4) The level of one of ordinary skill,
5) The level of predictability in the art,
6) The amount of direction provided by the inventor,
7) The existence of working examples,
8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The instant invention is drawn to a method of treatment, prevention or alleviation of a disease or a disorder or a condition of a living anima body, including a human, which disorder disease or condition is responsive to modulation of cholinergic receptors using a therapeutically effective amount of an azabicyclic aryl derivative of formula (I).

The state of the prior art: "A review with 123 refs. Elderly people are more likely than younger patients to develop cognitive impairment as a result of taking medications. This reflects age- and disease-associated changes in brain neurochem. and drug handling. Delirium (acute confusional state) is the cognitive disturbance most clearly associated with drug toxicity, but dementia has also been reported. The etiol. of cognitive impairment is commonly. Multifactorial, and it may be difficult to firmly establish a causal role for an individual medication. In studies of elderly hospital patients, drugs have been reported as the cause of delirium in 11 to 30% of cases. Medication toxicity occurs in 2 to 12% of patients presenting with suspected dementia. In some cases CNS toxicity occurs in a dose-dependent manner, often as a result of interference with neurotransmitter function. Drug-induced delirium can also occur as an idiosyncratic complication. Finally, delirium may occur secondary to iatrogenic complications of drug use. Almost any drug can cause delirium, especially in a vulnerable patient. Impaired cholinergic neurotransmission has been implicated in the pathogenesis of delirium and of Alzheimer's disease. Anticholinergic medications are important causes of acute and chronic

confusional states. Nevertheless, polypharmacy with anticholinergic compds. is common, especially in nursing home residents. Recent studies have suggested that the total burden of anticholinergic drugs may determine development of delirium rather than any single agent. Also, anticholinergic effects have been identified in many drugs other than those classically thought of as having major anticholinergic effects. Psychoactive drugs are important causes of delirium. Narcotic agents are among the most important causes of delirium in postoperative patients. Long-acting benzodiazepines are the commonest drugs to cause or exacerbate dementia. Delirium was a major complication of treatment with tricyclic antidepressants but seems less common with newer agents. Anticonvulsants can cause delirium and dementia. Drug-induced confusion with nonpsychoactive drugs is often idiosyncratic in nature, and the diagnosis is easily missed unless clinicians maintain a high index of suspicion. Histamine H2 receptor antagonists, cardiac medications such as digoxin and b-blockers, corticosteroids, non-steroidal anti-inflammatory agents and antibiotics can all cause acute, and, less commonly, chronic confusion. Drug-induced confusion can be prevented by avoiding polypharmacy and adhering to the saying "start low and go slow". Special care is needed when prescribing for people with cognitive impairment. Early diagnosis of drug-induced confusion, and withdrawal of the offending agent or agents is essential." (Moore et al., Drugs & Aging (1999), 15(1), pages 15-28).

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects, whether or not the compounds of formula of claim 1 would be useful for treating a pharmacological condition in a subject.

Amount of guidance/working examples: On pages 18-19 of the specification, applicant has example of inhibition of H-α-Bungarotoxine biding and the test compounds. However, applicant has not guidance or examples for treating any and all known and unknown disease using the compounds of formula (I).

The breadth of the claims: The breadth of claims is drawn to a method of treatment, prevention or alleviation of a disease or a disorder or a condition of a living anima body, including a human, which disorder disease or condition is responsive to modulation of cholinergic receptors using a therapeutically effective amount of an azabicyclic aryl derivative of formula (I).

The quantity of undue experimentation needed: Since the guidance and teaching provided by the specification is insufficient for treating a disease or a disorder or a condition of a living anima body, including a human, which disorder disease or condition is responsive to modulation of cholinergic receptors, one of

ordinary skill in the art, even with high level of skill, is unable to use the instant compounds as claimed without undue experimentation.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Taking all of the above into consideration, it is not seen where the instant claims 30-38, for treating a method for treating a disease or a disorder or a condition of a living anima body, including a human, which disorder disease or condition is responsive to modulation of cholinergic receptors using a compound of formula I according to claim 1, have been enabled by the instant specification.

5. Claims 30-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being possibly enabling for treating specific diseases, does not reasonably provide enablement for preventing diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established prophylactics are vaccines not the compounds such as present here. In addition, it is presumed that "prevention" of the claimed diseases would require a method of identifying those individuals who will develop

the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before occurs. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The passage spanning line 25, page 13 to line 38, page14 lists the diseases Applicant intend to treat. 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to medical treatment and are therefore physiological in nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become afflicted before the fact. 6) The artisan using Applicants invention would be a Board Certified physician who specialized to treat diseases with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of disorder diseases

generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent disorders generally. That is, the skill is so low that no compound effective generally against disorders has ever been found let alone one that can prevent such conditions. 7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not just those undergoing therapy for the claimed diseases and on the multitude of compounds embraced by Formula (I).

The Examiner suggests deletion of the word "prevention".

6. *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject

matter, which was not describe in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification lacks description of the claims i.e. "modulation of cholinergic receptor". An individual compound can either enhance or inhibit the receptor effect but not both simultaneously. Compounds of the claims were described in the specification to have inhibition of H-α-Bungarotoxine binding. Therefore, the specification lacks description of "modulation".

7. *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 11, 16-22, and 29-38 are rejected under 35 U.S.C. 102(a) as being anticipated by Hinshaw et al., J. Med. Chem., 2003, Vol. 46, pages 4240-4243. Hinshaw et al. discloses the instant claimed compound on page 4241, formula (I), which anticipates the instant compounds when L' is O , A is aromatic mono carbocyclic, B is covalent bond, L" is –CO_, and C is aromatic monocyclic carbocyclic in the instant application. Therefore, the instant claims are anticipated by Hinshaw et al.

8. Claims 1-6, 11, 16-22, and 29-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al., Bioorganic & Medicinal Chemistry Letters, 2001, Vol. 11, pages 2213-2216. Brown et al. discloses the instant claimed compound on page 2213, formula 3, which anticipates the instant compounds when L' is O , A is aromatic mono carbocyclic, B is covalent bond, L" is –CO_, and C is aromatic monocyclic carbocyclic in the instant application. Therefore, the instant claims are anticipated by Brown et al.

9. Claims 1-6, 11, 16-22, and 29-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al., J. Med. Chem. 1999, Vol. 42, pages 1306-1311. Brown et al. discloses the instant claimed compound on page 1307, formula 13a, 13b, 13c and page 1309, formula 18a, which anticipates the instant compounds when L' is O , A is aromatic mono carbocyclic, B is covalent bond, L" is –CO_, and C is aromatic monocyclic carbocyclic in the instant application. Therefore, the instant claims are anticipated by Brown et al.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Niloofar Rahmani whose telephone number is 571-272-4329. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/NILOOFAR RAHMANI/

06/16/2008

/D. Margaret Seaman/

Primary Examiner, Art Unit 1625